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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
31671-173265

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
09/889,321	July 13, 2001

First Named Inventor: Yousuke TAKAHAMA et al.

Art Unit	Examiner
1632	A. Wehbe

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record. Registration number 36,830.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

Ann S. Hobbs, Ph.D.
Typed or printed name

202-344-4651
Telephone number

February 21, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Yousuke TAKAHAMA et al.	Art Unit: 1632
Appln. No. 09/889,321	Examiner: A. Wehbe
Filed: July 13,2001	Atty. Docket No. 31671-173265
For: METHOD OF ACQUIRING IMMUNOLOGICAL TOLERANCE	Customer No. *26694* PATENT TRADEMARK OFFICE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop: AF amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the final Office Action issued October 21, 2005, and further to the Amendment filed January 23, 2006, Applicants submit the following remarks. In a telephone call to the Examiner today, the undersigned learned that the Examiner has not yet acted on the January 23, 2006 Amendment.

Rejection under 35 USC § 112, second paragraph

In the amendment filed January 23, 2006, claim 9 was amended as suggested by the Examiner. It is presumed that the amendment will be entered, as it overcomes the rejection of claim 9 for indefiniteness and reduces the issues for appeal.

Rejection under 35 USC §103

Claims 1-12 stand rejected under 35 USC §103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462. This rejection is traversed for the following reasons.

Specifically, the Examiner states, "the combination of the teachings of the cited

references provides motivation and a reasonable expectation of success for using transfected immature T lymphocytes to induce tolerance to foreign gene products expressed from the immature T lymphocyte".

In response to the above statement, Applicants explained that none of the Examiner's cited documents of DeMatteo et al., Bakker et al. and Ilan et al. describes the constituent feature of the instant invention, that is, "acquired immunological tolerance can be induced by using the above mechanism of acquiring immunological tolerance in the process of differentiation of the 'immature T lymphocytes' in thymus, by integrating genes expressing antigen into the 'immature T lymphocytes' and introducing the 'immature T lymphocytes' into thymus", and that the combination of the above cited documents lacks the description teaching the above structure, and therefore does not teach the instant invention. In short, it is clear that when each of the cited documents individually fails to teach the essential features of the instant invention, i.e. introducing an immature T lymphocyte transfected with specific foreign DNA into thymus in order to induce immunological tolerance, that the combination of documents will not teach or suggest the invention.

The Examiner stated that Ilan et al. is cited for "teaching the administration of cells transduced with the recombinant adenovirus" (Office Action of May 5, 2005, page 4, second paragraph). However, as Applicants have previously noted, Ilan et al. did not use immature T lymphocyte transfected with specific foreign DNA, nor is there any suggestion of this feature.

The Examiner further stated that DeMatteo et al. teaches that adenovirus is capable of infecting fetal T lymphocytes, and that Bakker et al. teaches methods of infecting fetal T lymphocytes *in vitro*. It is the Examiner's view that a person of skill in the art would be motivated to combine these references and achieve the present invention. Applicants respectfully disagree. Specifically, Applicants submit that there is no suggestion in either De Matteo et al. or Bakker et al. that would remedy the failure of Ilan to teach or suggest that immature T-lymphocytes be transfected with foreign DNA and introduced into thymus.

The Examiner stated that "specifically, DeMatteo et al. was cited to supplement the teaching of Ilan et al., by teaching that adenovirus is capable of infecting fetal T lymphocytes in fetal thymus and further that the transduced fetal T lymphocytes induce tolerance (DeMatteo et

al., page 5330, abstract, and Figure 1)." However, Applicants respectfully submit that, as DeMatteo et al. does not describe "fetal thymus," this conclusion of the examiner is not correct.

The Examiner also stated, "motivation to substitute fetal T lymphocytes for hepatocytes in the methods of Ilan et al. is provided by Bakker et al." Applicants respectfully disagree.

As described in the cited reference, Bakker et al. discloses use of a novel technique combining "adenovirus-mediated gene transfer" and "fetal thymic organ culture (FTOC)" "to determine at which stage of fetal thymic development NF-κB is critical" (for example, see abstract, page 3456, 10th to 7th lines from the bottom). In other words, this reference discloses that adenovirus-mediated introduction is employed when a gene is introduced into "fetal thymic organ culture". The examiner has stated: "motivation to substitute fetal T lymphocytes for hepatocytes" is provided by Bakker et al. However, as Bakker et al. does not disclose or suggest that gene-transferred cells are further used for gene transfer, it is respectfully submitted that Bakker et al. provides no such motivation.

In response to Applicants' argument that none of the documents of DeMatteo et al., Bakker et al. and Ilan et al. describes or teaches the constituent feature of the present invention, that is, "integrating genes expressing antigen in immature T lymphocytes and introducing the immature T lymphocytes into thymus", the Examiner, in the final office action, provides her reason why the cited documents teach constituent matters of the instant invention by stating, "to supplement the teachings of Ilan et al., the rejection of record relies first of the teachings of DeMatteo et al. who teaches that adenovirus is capable of infecting immature T Lymphocytes in neonatal thymus and further that the transduced neonatal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and figure 1). Note in particular that DeMatteo et al. teaches that it is the expression of the transgene in the neonatal T lymphocytes before maturation that induces tolerance. It was also noted in the rejection of record that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2)".

Applicants respectfully disagree with the Examiner's interpretation of DeMatteo et al. Applicants respectfully point out that DeMatteo does not transfect and introduce an immature T-lymphocyte, but directly injects adenovirus into the thymus. As described for example in the

abstract (page 5330) of DeMatteo et al., "Mice were inoculated in the thymus with a recombinant adenovirus containing the lacZ marker gene during the neonatal period at a time before T-cell maturation had occurred". This is completely different from the description of the instant invention describing "integrating genes expressing antigen in immature T lymphocytes and introducing the immature T lymphocytes into thymus". The description of DeMatteo et al. only describes that recombinant adenovirus containing a marker gene is inoculated into thymus during the neonatal period at a time before T-cell maturation had occurred. The present instant invention describes and claims " providing an immature T lymphocyte transfected with the foreign DNA; and introducing the immature T lymphocyte into thymus."

The Examiner further states, "note in particular that DeMatteo et al. teaches that it is the expression of the transgene in the neonatal T lymphocytes before maturation that induces tolerance". DeMatteo et al., however, only describes integration of adenovirus into thymus and the importance of the neonatal period in inducing immunological tolerance, and does not mention at all providing an immature T lymphocyte transfected with foreign DNA. Therefore, it is respectfully submitted that the Examiner's view is incorrect. This is because although the cells infected with adenovirus by the method of DeMatteo are cells in the thymus, they specifically represent epithelial cells or dendritic cells in thymus and not T lymphocytes, or immature T lymphocytes or thymocytes in thymus. Thus, DeMatteo at al. does not refer to integration of genes into T lymphocytes, as is presently claimed.

The Examiner further stated, "it was also noted in the rejection of record that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2)". Applicants note that DeMatteo et al., page 5334, column 2 only describe, "A cellular carrier was needed to trap the virus in the thymus to avoid immune sensitization" and does not teach that immature T lymphocytes transfected with foreign DNA should be introduced to provide this protection. It is clear that DeMatteo does not teach the constituent feature of the instant invention, that is, "integrating genes expressing antigen in immature T lymphocytes and introducing the immature T lymphocytes into thymus".

For all of the above reasons, it is respectfully submitted that the Examiner's

characterization of DeMatteo et al. is incorrect, and that DeMatteo et al. does not remedy the failure of Ilan et al. to teach or suggest that immature T-lymphocytes be transfected with foreign DNA and introduced into thymus, as taught and claimed in the present application.

In conclusion, even when the disclosures of Ilan et al., DeMatteo et al., and Bakker et al., are considered together, the present invention is not taught by the combination. Therefore, it is respectfully requested that the rejection of claims 1-12 under 35 U.S.C.103 (a) as being unpatentable over Ilan et al. (1996), in view of DeMatteo et al. (1997), and further in view of Bakker et al. (1999) be withdrawn.

Respectfully submitted,

Date: 2/21/06

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